CLAIMS

What is claimed is:

1. A method for screening a plurality of compounds for an ability to bind to a heterodimer of EGFR and another ERBB family member, the method comprising:

(a) contacting a first structure comprising an EGFR/ERBB heterodimer with a first solution, the first solution comprising the plurality of compounds;

(b) removing any compounds bound to the first structure to produce a second solution;

(c) contacting a second structure comprising an EGFR homodimer with the second solution, wherein the first structure and the second structure are identical except that the second structure does not contain an ERBB family member other than EGFR; and

(d) recovering any unbound compounds to produce a third solution,

whereby a compound that binds to a heterodimer of EGFR and another ERBB family member is identified.

2. The method of claim 1, wherein the plurality of compounds comprises a plurality of antibodies.

3. The method of claim 2, wherein the plurality of compounds comprises phage-displayed antibodies.

4. The method of claim 3, wherein the plurality of compounds comprises a phage-displayed antibody library.

5. The method of claim 4, wherein the phage-displayed antibody library comprises a phage-displayed single chain variable fragment (scFv) library or a phage-displayed Fab library.

6. The method of claim 3, wherein the phage-displayed antibodies are humanized.

7. The method of claim 1, wherein the first structure and the third structure comprise a cell that expresses EGRF and another ERBB family member, or an isolated membrane fraction of said cell.

8. The method of claim 7, wherein the cell is a recombinant cell that does not normally express any ERBB family member or ErbB ligand, but has been engineered to express a human EGFR and at least one other human ERBB family member.

9. The method of claim 1, wherein the second structure comprises a cell that expresses EGRF but no other ERBB family member, or an isolated membrane fraction of said cell.

10. The method of claim 9, wherein the cell is a recombinant cell that does not normally express any ERBB family member or ErbB ligand, but has been engineered to express a human EGFR.

11. The method of claim 1, further comprising:

(a) contacting a third structure comprising an EGFR/ERBB heterodimer with the third solution; and

(b) detecting binding of a compound to the EGFR/ERBB heterodimer on the third structure.

12. The method of claim 1, further comprising negatively selecting the plurality of compounds by contacting the plurality of compounds with a structure that is identical to the first and second structures except that it does not contain any ERBB family members.

13. A compound identified by the method of claim 1.

14. A method for suppressing the growth of a tumor associated with EGFR heterodimer activity in a subject, the method comprising administering to the subject bearing the tumor associated with EGFR heterodimer activity an effective amount of a compound of claim 13, whereby growth of the tumor is suppressed.

15. The method of claim 13, wherein the compound comprises an antibody or antibody fragment.

16. The method of claim 15, wherein the antibody or antibody fragment is a single chain fragment variable (scFv) antibody or an Fab antibody.

17. The method of claim 14, wherein the tumor is selected from the group consisting of benign intracranial meningiomas, arteriovenous malformation, angioma, macular degeneration, melanoma, adenocarcinoma,

malignant glioma, prostatic carcinoma, kidney carcinoma, bladder carcinoma, pancreatic carcinoma, thyroid carcinoma, lung carcinoma, colon carcinoma, rectal carcinoma, brain carcinoma, liver carcinoma, breast carcinoma, ovary carcinoma, solid tumors, solid tumor metastases, angiofibromas, retrolental fibroplasia, hemangiomas, Karposi's sarcoma, head and neck carcinomas, and combinations thereof.

18. The method of claim 14, wherein the subject is a mammal.

19. The method of claim 18, wherein the mammal is a human.

20. A method for identifying an antibody that specifically binds to an EGFR heterodimer, the method comprising:

(a) isolating a membrane fraction of a cell, wherein the membrane fraction of the cell comprises EGFR and at least one of ERBB2, ERBB3, and ERBB4 ;

(b) immunizing a mammalian subject with the membrane fraction; and

(c) purifying an antibody from the antisera that specifically binds to an EGFR heterodimer.

21. The method of claim 20, wherein:

(i) the cell is a mammalian cell that does not normally express any member of the ERBB family; and

(ii) the mammalian cell has been transformed with one or more expression constructs that encode one or more ERBB family members selected from the group consisting of EGFR, ERBB2, ERBB3, and ERBB4, wherein the transforming results in the mammalian cell expressing EGFR and at least one of ERBB2, ERBB3, and ERBB4 in a membrane of the cell.

22. The method of claim 20, further comprising:

(i) isolating spleen cells from the mouse immunized with the membrane fraction;

(ii) generating hybridomas using the spleen cells; and

(iii) identifying a hybridoma that produces a monoclonal antibody that specifically binds to an EGFR heterodimer.

23. A method for identifying a compound that inhibits formation of a heterodimer between EGFR and another ERBB family member, the method comprising:

(a) producing a first solution comprising a plurality of molecules that bind to EGFR;

(b) producing a second solution comprising a plurality of molecules that bind to the other ERBB family member;

(c) contacting the first solution with a first structure comprising a plurality of EGFR homodimers under conditions sufficient to allow any of the plurality of molecules to bind to the EGFR homodimers;

(d) contacting the second solution with a second structure comprising a plurality of homodimers of the other ERBB family member under conditions sufficient to allow any of the plurality of molecules to bind to the homodimers of the other ERBB family member;

(e) pooling any unbound compounds from the first and second solutions to produce a third solution; and

(f) testing the unbound compounds in the third solution for an ability to inhibit formation of a heterodimer between EGFR and the other ERBB family member, whereby a compound that inhibits formation of a heterodimer between EGFR and the other ERBB family member is identified.

24. The method of claim 23, wherein the first solution and the second solution comprise polyclonal antisera produced by immunizing an animal with purified EGFR, the other ERBB family member, or combinations thereof.

25. The method of claim 23, wherein the first solution and the second solution comprise pooled monoclonal antibodies produced by hybridomas generated from an animal that had been immunized with purified EGFR, the other ERBB family member, or combinations thereof.

26. The method of claim 23, wherein the first solution and the second solution are the same.

27. The method of claim 23, wherein the EGFR is human EGFR and the other ERBB family member is human ERBB2.

28. The method of claim 23, wherein the first structure and the second structure each comprises a cell that has been engineered to express either EGFR or the other ERBB family member.